Analytic Dilemmas: E.g.: The Woman's Health Initiative

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Topics

- Arguments by analogy and observation
- Surrogate endpoints
- Analysis as randomized (ITT)
- Multiplicity
- Interim analysis
- Subgroups

The WHI- HRT Component

- Four studies: Diet, CaD, ERT, PERT
- One DSMB: 12 members
- We recently recommended closing the PERT
  - significantly increased rate of breast cancer
  - unfavorable balance of risks and benefits

Analogy and epidemiology

- HRT question: Does HRT prevent heart attacks?

Background

- Women make estrogen; men don't
- Women's rate of heart attack lower than men's…until
- Menopause…when they stop producing estrogen
- Therefore, giving estrogen will reduce rate of heart attack

Experiment

- CDP, a study in men, had an estrogen arm
- Men on the estrogen arm had increased rate of MI (about 30%)
- Arm ended early
- Conclusion: estrogen is bad for men, good for women

Epidemiology

- Women on HRT have roughly a 50% reduction in rate of heart attack
- NON-RANDOMIZED
- How do we know those on HRT are the "same" as those not on HRT?

Surrogates

- If HRT really reduces rate of heart attack, we should see benefit on risk factors.
- PEPI: several different formulations of HRT
- Showed benefit on risk factors

WHI Question

- For post-menopausal women, does addition of hormones (ERT or PERT) lead to overall benefit ?
  - Decrease in heart attack, hip fracture, colorectal cancer
  - Increase in invasive cancer, PE
  - No effect on death from other cause

IOM's Answer

- The answer is in
- The study is expensive, unnecessary, and unethical because it puts women on placebo at unnecessary risk

DSMB's Response

- You, IOM, may know the answer
- We, the DSMB, don't
- The study needs to be done to answer a very important question

Analysis as Randomized

- We knew that people would not comply
- Therefore, the sample size incorporated expected cross-over
- Cross-over likely to attenuate both benefit and harm
- Had we analyzed as-treated, we would have added an observational component (and that is EXACTLY what we didn't want)

The Dilemma

- I am curious yellow (we want to know):
  - If women TAKE their HRT, do they get reduced event rate?
- But, I am curious blue (we are actually asking):
  - If women are RANDOMIZED to HRT, is their event rate

The Experiment

- We randomize to achieve balance
- People stop taking their study medication
  - The drop-outs are not random
  - We cannot assume they are equal in the two groups

Multiplicity

- Torture the data until they confess. –anon
- You increase the probability of finding a statistically significant result by:
  - Look over and over
  - Look at many endpoints

Our Approach

- Adjust p-value for multiple endpoints
- Adjust p-value for multiple looks
- Decide what scenario would make us stop

BUT

- No scenario posited increased risk for CHD
- General moral: position yourself for the unexpected

Subgroup analysis

- Multiplicity inflates Type I error rate
- Inefficient (ignores much of the data)
- Some subgroups very small

Cox Modeling of Time to Event

- Cox model to look at interactions

Comments

- Subset analysis not reliable.
- Cox modeling highly model dependent

For early stopping…

- We need consistency of subgroups
  - HERS-like and without CHD
  - By age
  - By demographic groups

How do we know whether effect over time?

- Hazard ratio:

Year	1	2	3	4	5
	1.5	1.2	1.0	.9	.9

Cumulative

- **Hazard ratio:**

Year	1	2	3	4	5
Annual	1.5	1.2	1.0	.9	.9
Cum	1.5	1.3	1.2	1.1	1.1